Heart & Lung xxx (2017) 1–7

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

Late mitral restenosis after percutaneous commissurotomy: Predictive value of inflammation and extracellular matrix remodeling biomarkers

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ARTICLE INFO

Article history:
Received 1 January 2017
Received in revised form
28 February 2017
Accepted 25 March 2017
Available online xxx

Keywords:
Mitral stenosis
Percutaneous mitral commissurotomy
Chronic inflammation
Matrix metalloproteinases
TNFα
Mitral restenosis

ABSTRACT

Background: The role of chronic inflammation in mitral restenosis after percutaneous mitral commissurotomy (PMC) is still controversial.
Aims: We sought to assess the predictive value of inflammation and extracellular matrix (ECM) remodeling biomarkers in late mitral restenosis after PMC.
Methods: We prospectively enrolled 155 patients (mean age 46.2±11 years) with at least 5 year follow up after primary PMC. Serum levels of high sensitive C-Reactive Protein (hs-CRP), matrix metalloproteinases MMPs, tissue-specific inhibitors of matrix metalloproteinases TIMPs, and tumor necrosis factor α (TNFα)] were measured.
Results: Late mitral restenosis occurred in 55 patients (35.5%). The independent predictors of late mitral stenosis were: age> 55 years [HR10.51 (95%CI 1.12−95.9); p=0.037]; no long acting penicillin therapy [HR 18.1 (95% CI 2.6−122.9); p=0.003]; TNFα > 80 ng/ml [HR 5.85 (95% CI 1.1−31.42); p=0.039]; and TIMP-2 > 289 ng/ml [HR 0.52 (95% CI 0.22−0.95); p=0.045].
Conclusion: Chronic inflammation and ECM remodeling are involved in late mitral restenosis after PMC.

Introduction

Rheumatic fever represents the most common etiology of mitral stenosis (MS). Although MS has greatly decreased in Western countries; it still results in significant morbidity and mortality worldwide.[1–3] Similar to other rheumatic valve disease, the acute lesion corresponds to direct consequences of excessive immunological reaction following a streptococcal infection; whereas, several years are often necessary for the development of significant MS.[3]

Surgical mitral commissurotomy (closed- or open-heart commissurotomy), had dramatically improved the short-term outcome of patients affected with rheumatic MS. However, despite satisfactory immediate commissurotomy result, the restenosis was almost inevitable at follow up.[4–6] Histologic examinations have demonstrated that mitral restenosis was essentially due to the formation of commissural fibrotic cicatrix.[6]

Since percutaneous mitral commissurotomy (PMC) was first described by Inoue in 1984,[7] its use has spread worldwide, and it is actually considered to be the treatment of choice for patients with MS and suitable valve anatomy.[8] Nonetheless, PMC is also hampered by late mitral restenosis and the need for further mitral valve re-intervention (either percutaneous or surgical). The mechanisms responsible for such an outcome appear to be multifactorial. Recently, chronic inflammation has been shown to be actively involved in mitral valve restenosis after PMC.[9]

The matrix metalloproteinases (MMPs) are zinc- and calcium-based proteolytic endopeptidases produced by inflammatory cells and playing a central role in remodeling of the extracellular matrix (ECM) in both physiological and pathological states.[10] The MMPs

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECM, extracellular matrix; hs-CRP, high sensitive C-Reactive Protein; HR, hazard ratio; LAP, long acting penicillin; MMP, matrix metalloproteinases; MS, mitral stenosis; MVA, mitral valve area; NYHA, New York Heart Association; PMC, percutaneous mitral commissurotomy; PASP, pulmonary artery systolic pressure; TIMP, tissue-specific inhibitors of matrix metalloproteinases; TNF, tumor necrosis factor; TTE, transthoracic echocardiography.

Conflicts of interest: None to declare.

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0147-9563/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.hrtlng.2017.03.006

are inhibited by tissue-specific inhibitors of matrix metalloproteinases (TIMPs). An increase in the levels of certain MMPs, or a decrease in their TIMPs, has been implicated in the cause of ECM breakdown.[10,11] Tumor necrosis factor-α (TNFα) represents a potent pro-inflammatory cytokine that stimulates the secretion of MMPs. Serum levels of both MMPs and TNFα were shown to be increased in the presence of rheumatic MS.[12,13]

In the current study, we aimed to assess the role of inflammation and ECM remodeling biomarkers in predicting late mitral restenosis after PMC.

Methods

Study population

From May 2005 to December 2010, 350 patients with rheumatic MS [mitral valve area (MVA) <1.5 cm^2] underwent a primary PMC. After the procedure, regular clinical and echocardiographic follow up was performed. The exclusion criteria were as follows: a) unsatisfactory immediate result of PMC (defined as the absence of a total opening of at least one commissure or MVA <1.8 cm^2 immediately after PMC); b) mitral regurgitation $>$ grade II post PMC; c) associated aortic valve disease; d) chronic or acute inflammatory of infectious disease; e) neoplastic pathology; f) previous history of diabetes mellitus, coronary artery disease or chronic kidney disease (creatinine clearance <60 ml/min). All patients with at least 5 years of follow up without mitral restenosis, who did not meet any exclusion criteria were prospectively enrolled into the study (Fig. 1).

At the time of inclusion, blood tests were performed and compared to those of a control group including gender- and age-matched healthy subjects. Thereafter, clinical and echocardiographic follow-up was performed every 6 months, unless previously clinically indicated.

The study was carried out in accordance to the Helsinki declaration. The local ethics committee has approved the study protocol, and all patients provided written informed consent.

Percutaneous mitral commissurotomy

All PMC procedures were performed by the same experienced operator (R.M.) using the antegrade transvenous approach. After trans-septal puncture, mitral commissurotomy was performed using the Inoue balloon according to the stepwise technique under echocardiographic monitoring.

Clinical evaluation

The prescription of long acting penicillin (LAP) (during the last 12 months), and the presence of atrial fibrillation (AF) on electrocardiogram were investigated.

Blood handling and assays

Blood tests were performed in MS patients and healthy individuals, including complete blood count (with neutrophil-to-lymphocyte ratio assessment) and serum levels of high sensitive C-Reactive Protein (hs-CRP), MMPs (3 and 9), TIMPs (1 and 2) and TNFα.

Serum levels of MMPs and TIMPs

Immediately after collection, the blood was allowed to clot at room temperature and then centrifuged at 300× g at room temperature for 20 min. The serum was then removed and stored at −80 °C until batched analysis was performed. Enzyme-linked immunoassays were performed to measure levels of MMP-3, and MMP-9 using commercially available kits (Quantikine, R&D Systems, USA).

Serum levels of TNFα

All blood samples were immediately transferred to an evacuated tube containing 3.8% buffered sodium citrate. Plasma fractions were obtained by centrifugation of these mixtures for 10 min at 2000 rpm at room temperature, and stored at −20 °C until the assay. Plasma levels of TNFα were measured using a commercially available enzyme-linked immunosorbent assay kit (Bender Med Systems, Vienna, Austria).

Echocardiographic assessment

In all patients, a transthoracic echocardiography (TTE) was performed at the time of inclusion (the same day of blood sampling) using the Vivid 9 device (General Electric Healthcare, NY, USA). The standard echocardiographic measurements were done and averaged in 4 cardiac cycles. These measurements were taken while the patient was on supine and left lateral decubitus positions. MVA (planimetry) was measured in parasternal short-axis view. Continuous wave Doppler measurements were taken at a speed of 100 mm/s. The values from 5 consecutive beats were averaged to measure transmitral pressure gradient using Bernoulli equation and pulmonary artery systolic pressure (PASP) from tricuspid regurgitation. Color Doppler was done to assess the degree of mitral

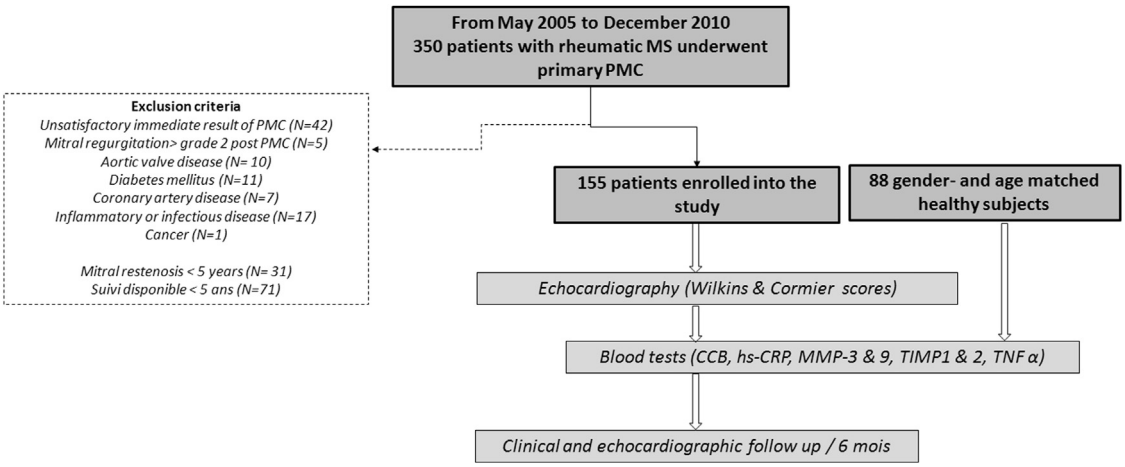

Fig. 1. Flow chart of the study population. Abbreviations: CBC = complete blood count; hs-CRP = high-sensitive C-Reactive Protein; LAP = long acting penicillin; MMP = matrix metalloproteinases; MS = mitral stenosis; PMC = percutaneous mitral commissurotomy; TIMP = tissue-specific inhibitors of matrix metalloproteinases; TNFα = tumor necrosis factor-α.